Importantly, the effect of CRV was similar in ischemic heart disease (risk reduced by 67%. P=0.003) and in nonischemic dilated cardiomyopathy (risk reduced by 67%. P=0.014). In conclusion, the addition of CRV to conventional therapy is associated with a substantial (67%) reduction in the mortality of patients with chronic CHF. The treatment effect is seen across a broad range of severity and etiology of disease.

As used herein, by "Class II CHF" is meant patients with cardiac disease resulting in slight or moderate limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain. By "Class III CHF" is meant patients with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain. By "Class IV CI" is meant patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. symptoms or cardiac insufficiency, or of the anginal syndrome. By "less than ordinary physical activity" is meant climbing, one flight of stairs, or walking two hundred yards.

Design of Study

Patients on background therapy with diuretics. ACE inhibitors and/or digoxin were stratified on the basis of baseline submaximal exercise performance, into one of four trials:

- study 220, a dose response study in moderate (NYHA II–IV) CHF with exercise testing as a primary endpoint
- study 221, a dose titration study in moderate (NYHA II–IV) CI with exercise testing as a primary endpoint
- study 239, a dose titration study in severe (NYHA III–IV) CHF with quality of life as a primary endpoint
- study 240, a dose titration study in mild (NYHA II–III) CHF with progression of CHF as a primary endpoint

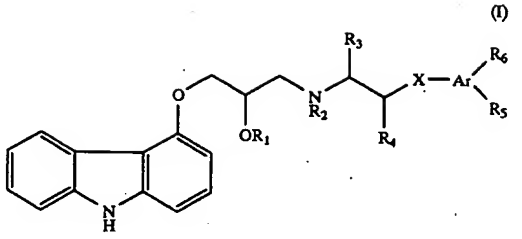
Sixty-four centers in the US participated in the trial program. All sites conducted protocols 239 and 240, while 33 performed protocol 220 and 31 performed protocol 221.

Although each trial had its own individual objectives, the overall program objective defined prospectively was evaluation of all-cause mortality. Based upon a projected enrollment of 1100 patients, the program had 90% power to detect a 50% reduction in mortality (two-sided) between carvedilol and placebo, assuming a mortality rate in the placebo group of 12% over the duration of the trials (α=0.05).

Randomization was preceded by a screening and challenge period common to the four protocols The purpose of the screening period was to quality patients for study entry obtain reproducible baseline measurements, and stratify patients into the appropriate trial based on submaximal exercise testing. During the challenge period, patients received low-dose open-label carvedilol (6.25 mg b.i.d.) for two weeks. Patients unable to tolerate this dose did not proceed to randomization. Patients tolerating low-dose carvedilol were then randomized to blinded medication (carvedilol or placebo) with the dose titrated over several weeks in the range of 6.25 to 50 mg b.i.d. (or equivalent level of placebo). The maintenance phase of each study ranged from six to 12 months, after which patients had the option of receiving open-label carvedilol in an extension study.

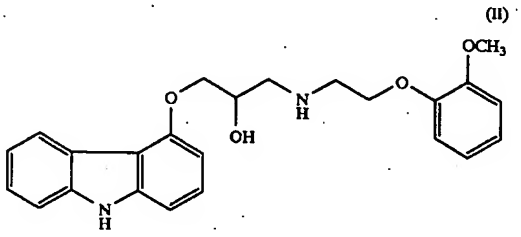
Results

The analysis presented below corresponds to the data set on which the DSMB made the recommendation to terminate the trials. Included in this intent-to-eat analysis are all patients enrolled in the US trials as of Jan. 20, 1995; 624 receiving carvedilol and 356 placebo. An analysis of baseline patient characteristics (Table 1) shows good balance between the randomized groups.



(I)

The overall mortality results for the program are shown in Table 2. All deaths that occurred during the intent-to-treat period are included. Treatment with carvedilol resulted in a 67% reduction in the risk of all-cause morality. Analysis of mortality by certain baseline characteristics shows this to be a broad effect regardless of severity or etiology of CI. The effect was uniform in patients with mild heart failure or moderate to severe heart failure. Similarly, the mortality reduction was equivalent in patients with ischemic or non-ischemic heart failure.



(II)

The foregoing is illustrative of the compounds of this invention. This invention, however, is not limited to the precise embodiment described herein, but encompasses all modification within the scope of the claims which follow.

We claim:

1. A method of decreasing mortality caused by congestive heart failure in a patient in need of such decrease, said method comprising:
   - administering to said patient first dosages at least daily for a period of from 7 to 28 days, said first dosages each comprising carvedilol,
   - then administering to said patient second dosages at least daily for a period of from 7 to 28 days, said second dosages each containing carvedilol, and
   - then administering to said patient third dosages daily for a maintenance period, said third dosages each comprising carvedilol, said third dosages each comprising a daily maintenance dose in the range of from about 10 mg to about 100 mg of carvedilol,
   - said first dosages each comprising carvedilol in an amount which is 10–30% of said daily maintenance dose,
   - said second dosages each comprising carvedilol in an amount which is 20–70% of said daily maintenance dose.

2. The method of claim 1, wherein the daily maintenance dose is about 25 mg or about 50 mg.

3. The method of claim 1, further comprising administering to said patient at least one other therapeutic agent selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics and cardiac glycosides.

4. The method of claim 3, wherein the angiotensin converting enzyme inhibitor is selected from the group consisting of captopril, lisinopril, fosinopril, enalapril and pharmaceutically acceptable salts of captopril, lisinopril, fosinopril and enalapril.

5. The method of claim 3, wherein said diuretic is selected from the group consisting of hydrochlorothiazide, torasemide, furosemide, and pharmaceutically acceptable salts of hydrochlorothiazide, torasemide and furosemide.

6. The method of claim 3, wherein said cardiac glycoside is selected from the group consisting of digoxin, β-methyl-digoxin and digitoxin.

7. A method of decreasing mortality caused by congestive heart failure in a patient, said method comprising administering to said patient first dosages once or twice daily, for a period of from 7 to 28 days, said first dosages each comprising carvedilol in an amount of about 3.125 mg or 6.25 mg,

then administering to said patient second dosages once or twice daily, for a period of from 7 to 28 days, said second dosages each comprising carvedilol in an amount of about 12.5 mg, and

then administering to said patient maintenance third dosages once or twice daily, said third dosages each comprising carvedilol in an amount of about 25.0 mg or about 50.0 mg.

8. A method as recited in claim 7, wherein at least one of said first, second and maintenance dosages further comprises at least one other therapeutic agent selected from the group consisting of an angiotensin converting enzyme inhibitor, a diuretic and a cardiac glycoside.

9. A method of treating to decrease mortality resulting from congestive heart failure in a patient in need of such treatment, said method comprising administering to said patient carvedilol, alone or in combination with at least one other therapeutic agent, in unit dosages once or twice daily, for a period of from 7 to 28 days, said unit dosages each comprising a pharmaceutical formulation comprising carvedilol in an amount of about 3.125 mg or about 6.25 mg.

10. A method of treating congestive heart failure in a patient in need of such treatment, said method comprising:

administering to said patient first dosages at least daily for a period of from 7 to 28 days, said first dosages each comprising carvedilol,

then administering to said patient second dosages at least daily for a period of from 7 to 28 days, said second dosages each comprising carvedilol, and

then administering to said patient third dosages daily for a maintenance period, said third dosages each comprising carvedilol, said third dosages each comprising a daily maintenance dose in the range of from about 10 mg to about 100 mg of carvedilol,

said first dosages each comprising carvedilol in an amount which his 10–30% of said daily maintenance dose,

said second dosages each comprising carvedilol in an amount which is 20–70% of said daily maintenance dose.

11. Method of claim 10, wherein carvedilol is administered to the patient once or twice daily.

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